Modeling the emergence of stage II retinal waves in immature retina

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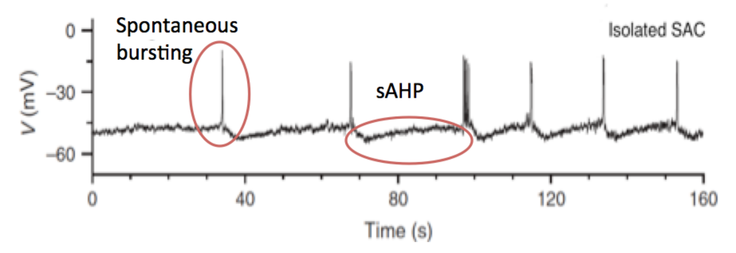
Abstract

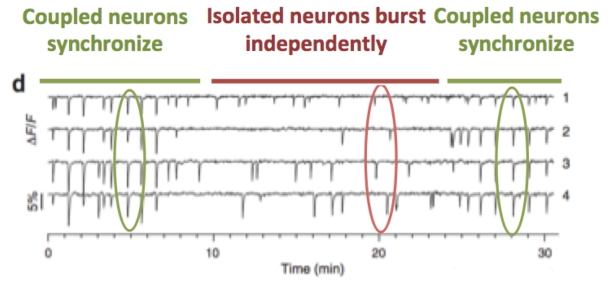
Retinal waves are spontaneous bursting activity propagating in the developping retina until vision is functional. In this work we propose a biophysical modelling of the mechanism that generates the spontaneous intrinsic cell-autonomous rhythmic bursting in Starburst Amacrine Cells (SACs), observed experimentally in [1] which is directly linked with the emergence of stage II retinal waves. We analyze this system from the dynamical system and bifurcation theory perspective.

Context & Motivation

Necessary components for the emergence of retinal waves [1]



Recording of spontaneous cell-autonomous rhythmic bursts in isolated SACs in rabbits [1].



Coupled SACs burst synchronously [1]

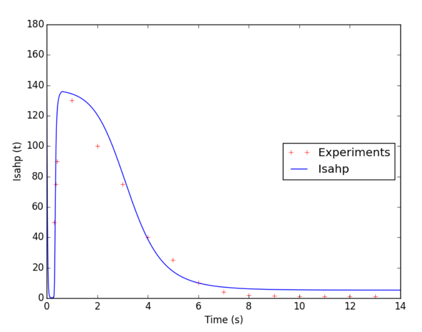
- Spontaneous rhythmic **bursting** activity of isolated SACs
- Refractory mechanism modulating the silent period of the bursting activity (slow After HyperPolarisation current, **sAHP**)
- **Coupling** via cholinergic synapses to ensure the necessary level of synchrony

Motivation & Goals

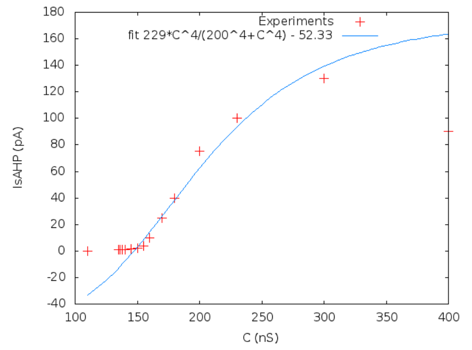
- Finding a biophysical modelling reproducing these experiments and generating waves by taking into account the biophysical mechanisms and tuning parameters from the biophysical literature.
- Propose a bifurcation analysis in order to extract a generic biophysical mecanism of the spontaneous bursting of isolated SACs.
- Model network interactions to reproduce propagating spatio-temporal patterns with two goals : i) Characterize the conditions for synchronization of neurons ii) Study the effect of the synaptic coupling on spatio-temporal patterns.

Fitting experimental curves

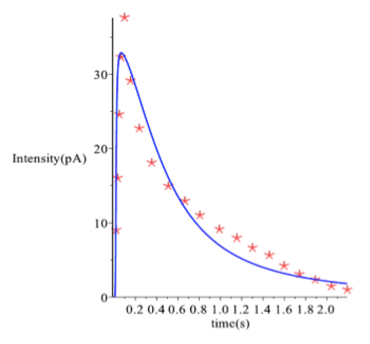
- Model sAHP according to [2] and extract the corresponding parameters by experimental fits and literature.
- For SACs, the kinetics of sAHP are the same as for pyramidal neurons but amplitudes are weaker.
- Extract the parameters for the cholinergic currents by fitting the experimental curves of Zhou et al. 2004.



$I_{sAHP}(t)$



$I_{sAHP}(C)$



$I_{Ach}(t)$

Acknowledgements

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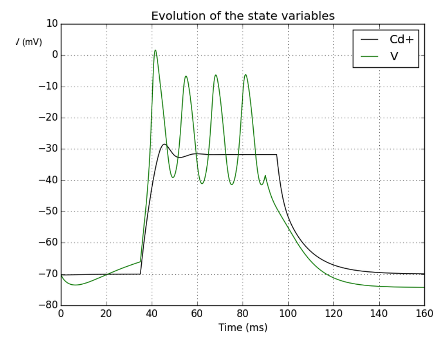
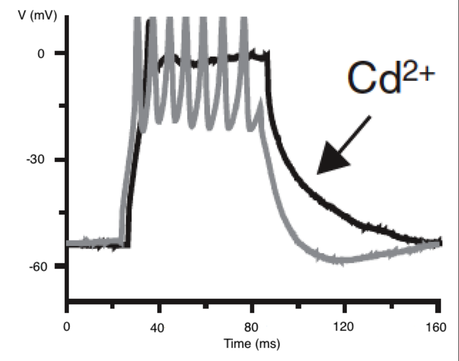
Modelling Cell-Autonomous Bursts



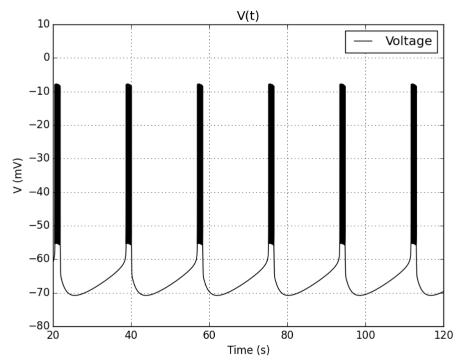
Model



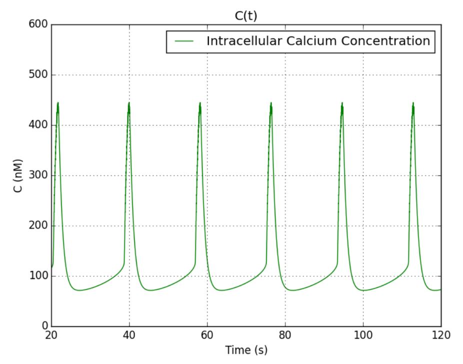
Experiment

- Modeling the ionic mechanism of intrinsic bursts according to [1] based on an extended M-L model.
- Fast oscillations of the voltage while applying an external current pulse of 150 pA followed by a subsequent AHP. Blocking all calcium related currents leads to the vanishing of both fast oscillations and AHP.

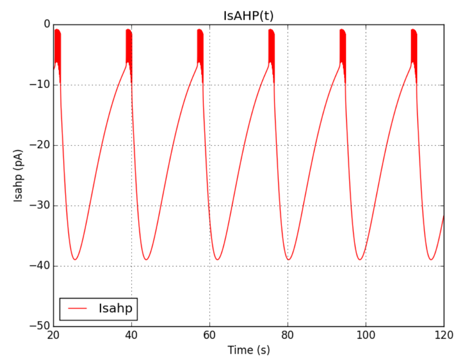
Simulations of isolated SACs



$V(t)$

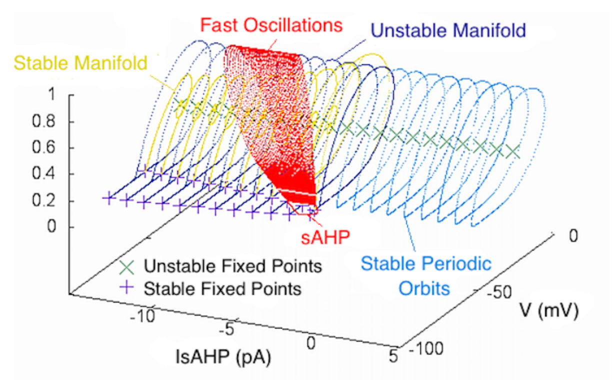


$C(t)$



$I_{sAHP}(t)$

Bifurcation Analysis for Isolated SACs

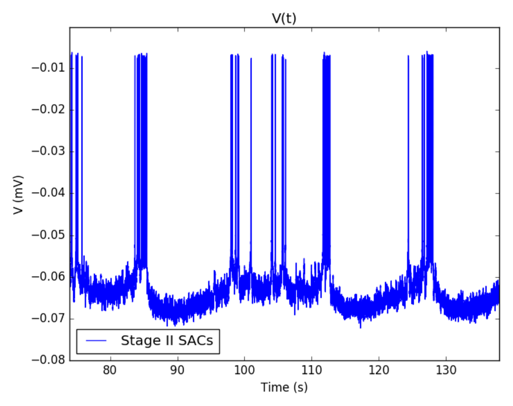


3D Bifurcation diagram of the mechanism generating rhythmic intrinsic bursts in SACs

Proposed biophysical process

- SACs are in a regime where they can oscillate spontaneously.
- As they oscillate, the calcium load increases, so the effect of sAHP increases up to a point where oscillations stop, reaching a steady state where the level of the voltage is quite lower.
- Then, intracellular calcium concentration unloads, I_{sAHP} decreases, until the effect of sAHP is small and oscillations start again.

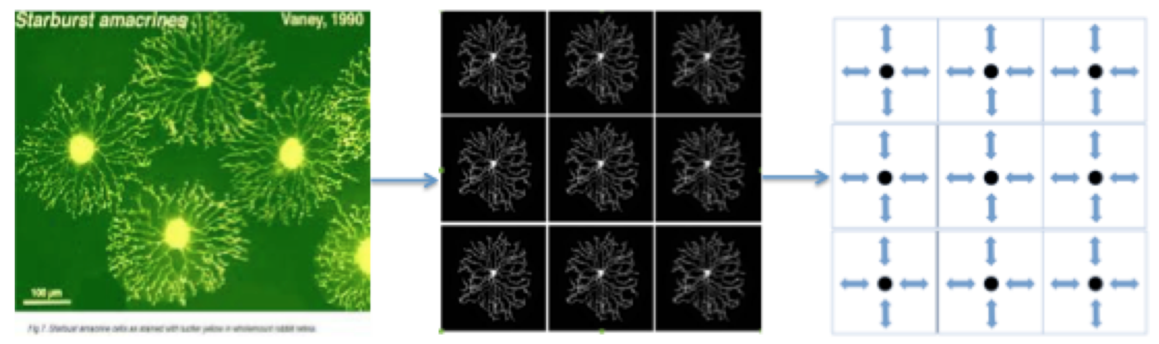
Adding Noise



Simulation adding Gaussian noise

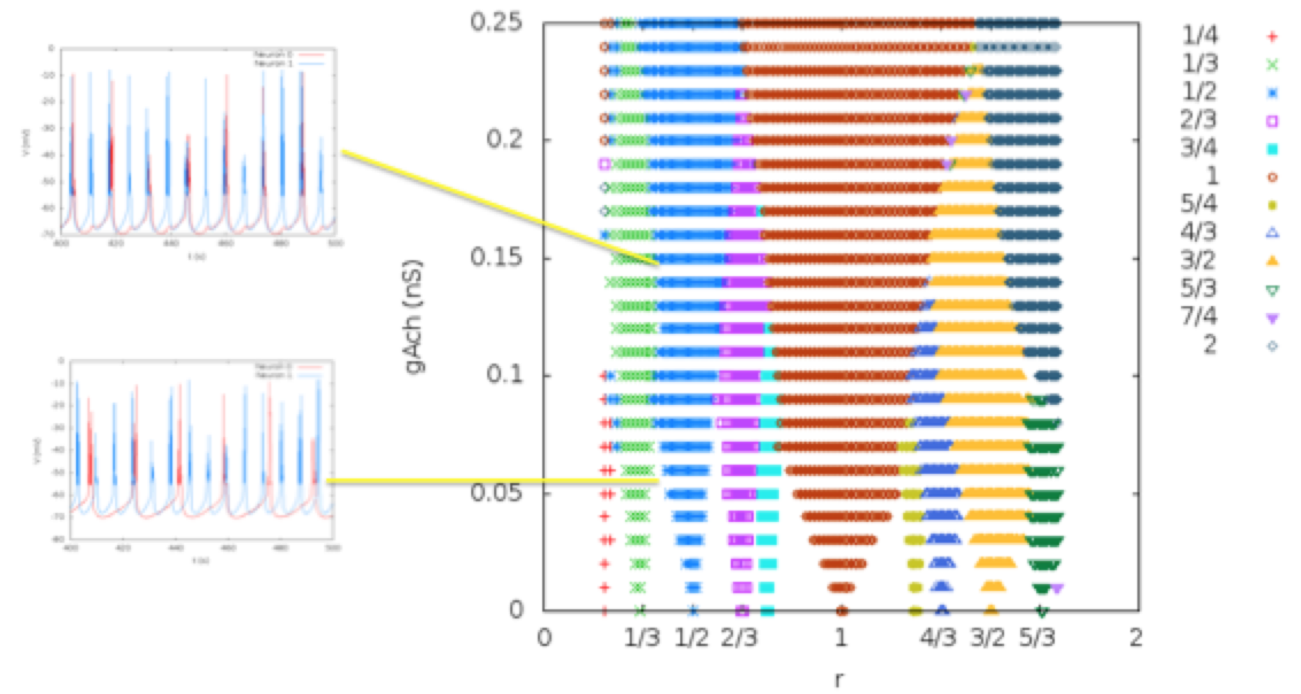
- Our model is deterministic and bursting period is regular.
- In order to break the regularity, we add a zero-mean Gaussian noise of $\sigma = 10pA$.
- Increasing the standard deviation of the noise we observed that bursting period decreases.

Modeling network interactions



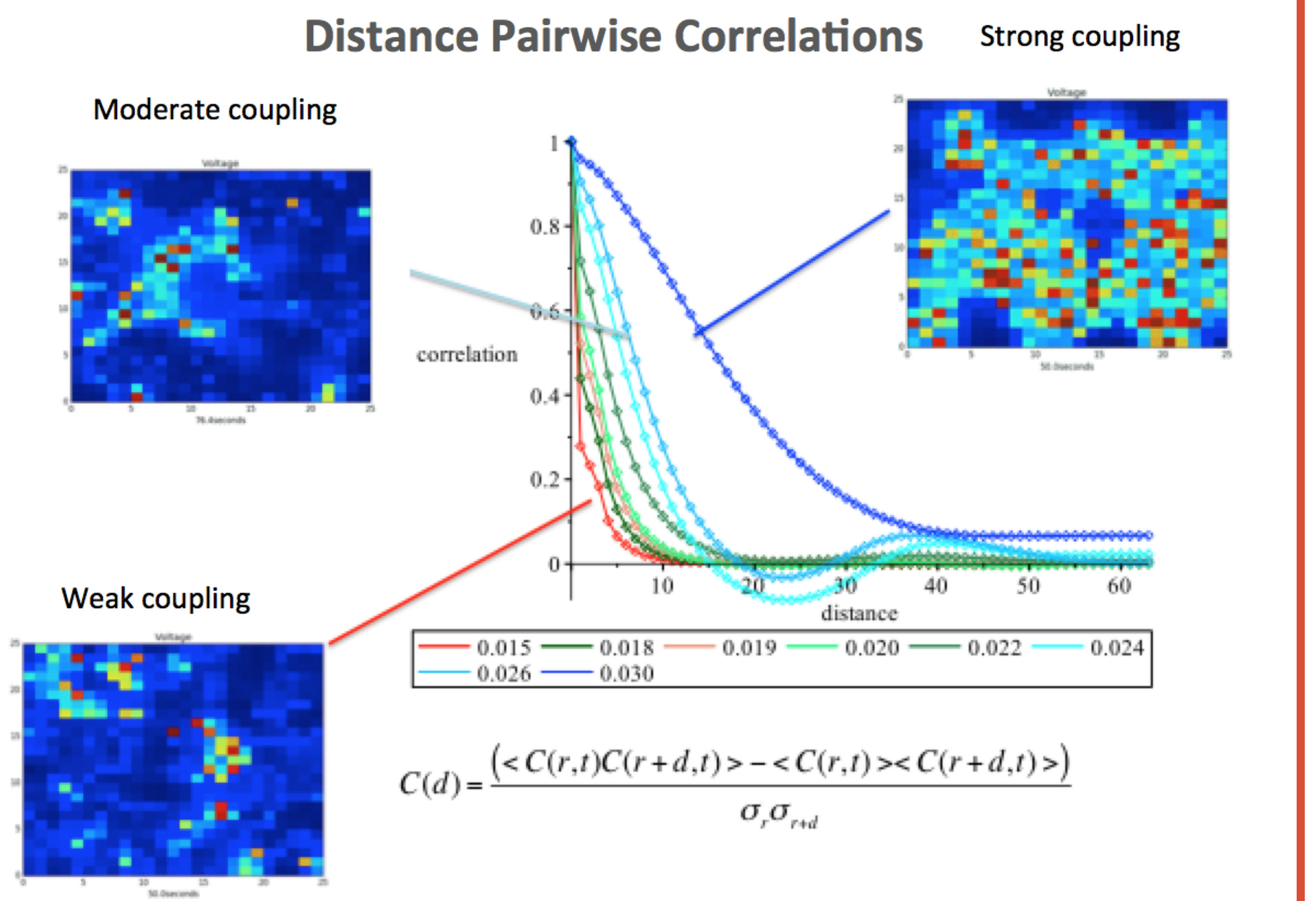
SACs realistic connections — SACs on a lattice — SACs become points on a lattice

- SACs are placed on a square lattice connected to their four nearest neighbours.
- Synapses are excitatory through cholinergic transmission.
- It is found experimentally that SACs are not identical, i.e. their characteristic refractory time follows a Gaussian distribution.



- Introducing a variability in the bursting period, we end up with a network of coupled bursters. In order to study the conditions for synchrony we start from the simpler case of two coupled neurons.
- As in the case of coupled oscillators, in our case we observe Arnold tongues.
- Starting from isolated neurons with a random ratio of bursting period, we observe that as we increase the strength of the coupling we obtain resonances at the closest rational numbers. Strong coupling would give 1:1 synchrony.

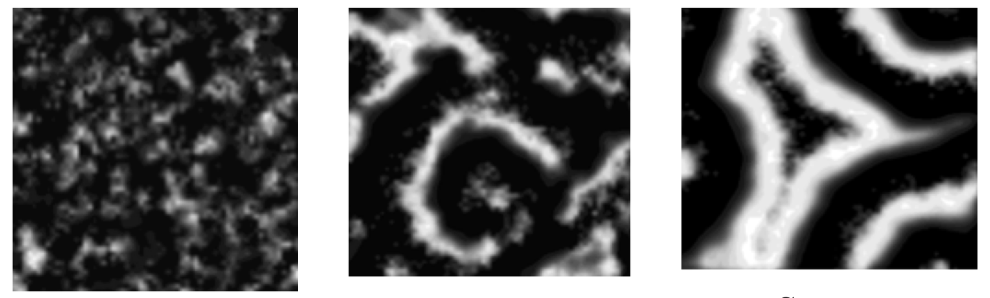
Network Simulations



$$C(d) = \frac{\langle C(r,t)C(r+d,t)\rangle - \langle C(r,t)\rangle\langle C(r+d,t)\rangle}{\sigma_r \sigma_{r+d}}$$

- Top: Network simulations for the Voltage of 625 neurons on a square lattice. Blue and red colours correspond to low and high activity respectively. Also, we compute the correlations with respect to the distance of cells.
- Bottom: Network simulations for the Calcium of 4096 neurons on a square lattice. Black and white colours correspond to low and high activity respectively.
- Weak coupling leads to localised bumps of activity. Strong coupling leads to complete synchrony. Moderate coupling leads to propagating patterns.
- We study pairwise correlations with respect to distnace. There is an intermediate regime where we observe anticorrelations. Anticorrelation corresponds to a region of hyperpolarization corresponding to the boundary of the wave.

Calcium Waves



Weak — Moderate — Strong

Conclusions & Future perspectives

- We proposed a biophysical modelling of the spontaneous intrinsic cell-autonomous rhythmic bursting in Starburst Amacrine Cells during stage II retinal waves, directly extracted from experimental and biophysical data.
- Our model is able to generate spontaneously the observed rhythmic bursting, without the need of any external excitation to trigger the system, as opposed to [3] and [4].
- With our model we are able to explain biophysically and dynamically how the slow oscillations are generated and sustained in developping SACs.
- We have shown by our modelling the network effect: there is a necessary level of synchrony to be achieved between neighbouring SACs to generate propagating waves.

References

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